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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
CANELLA, KAREN A	
ART UNIT	**PAPER NUMBER**
1643	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/27/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/767,018	STOCKWELL, BRENT R.	
	Examiner	Art Unit	
	Karen A. Canella	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *7-10,12,14-16 and 18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *7-10,12,14-16 and 18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/12/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Acknowledgment is made of applicants election of Group IV. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP '818.03(a)).

Claims 1-6, 11, 13, 17 and 19-66 have been canceled. Claims 10, 12 and 14 have been amended. After review of the prior art, the invention of Group II is hereby rejoined to the elected invention of Group IV. Claims 7-10, 12, 14-16 and 18 are pending and examined on the merits.

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 60/443,728, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. the '728 provisional application provides a written description of erastin which is the ethyl ester of claims 7-10, 14-16 and 18. Said application fails to provide written description of erastin B, which is the fluorophenyl compound of claims 7-9, 12, 14-16 and 18. The fluorophenyl erastin B is described in provisional application 60/482,688. Therefore claims 7-9, , 12, 14-16 and 18 which include the structure of erastin B will be given the effective filing date of June 25, 2003. Claim 10 which includes only the structure of erastin A will be given the effective filing date of January 29, 2003.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 7-10, 12, 14-16 and 18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims7-10, 14-16 and 18 are reliant on a genus of analogs of erastin. Claim 12 is reliant on a genus of analogs of erastin B. Stedman's Medical Dictionary, 27th Edition, defines a compounds which is an analog as "resembling another in structure, but not necessarily an isomer", and provides the example of 5FU being an analog of thymine (attachment). The specification provides no specific definition for the term "analog", therefore the conventional definition as used in the art will apply. The instant specification describes two compounds, erastin and erastin B that function selectively to inhibit the growth of cells expressing SV40 small T antigen, h-Ras, or both of SV40 small T and h-Ras. The compounds have obvious structural similarities, however, the specification does not provide a link between a portion of the structures of erastin and erastin B that is responsible for the selective growth inhibiting activity. Further, the specification fails to establish how the variant portion between erastin and erastin B contributes or does not contribute to the activity of the analogs.

Although drawn to the DNA arts, the conclusions of the Federal circuit in Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002) and University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) are relevant to the instant claims. The Enzo court adopted the standard that "the written description requirement can be met by 'show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure, other physical and/or

chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. " Id. At 1324, 63 USPQ2d at 1613. The Univ of California vs Lilly court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus.".

In the instant case, the specification fails to describe a "representative number" of analogs of erastin or erastin B because only the two aforesaid compounds are described. The specification also fails to make the required correlation between partial structure and function necessary to describe the genus of analogs .

Thus, the description of two members of the genus of analogs is insufficient to describe the claimed genus because the specification fails to characterize the genus of analogs by partial chemical structure linked to the required function and because two species are not a "representative number" of species. One of skill in the art would reasonably conclude that applicant was not in possession of the genus of analogs of erastin or erastin B and therefore was not in possession of the methods which relied on said analogs.

Claims 7-9, 14-16 and 18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of killing tumor cells in vitro, does not reasonably provide enablement for a method of treating or preventing cancer in an individual. both methods requiring erastin as a tumor-toxic agent. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 7-9 are drawn to a method of inducing death in tumor cells comprising contacting said cells with erastin, erastin-B or analogs of erastin. Claims 14-16 and 18 are drawn to a method of treating or preventing cancer in an individual comprising the administration of erastin, erastin-B or a compound which is an analogue of erastin. Claims 18 requires in part, the administration of at least one additional anti-tumor agent that inhibits growth of the tumor cells in a synergistic manner with the first agent.

(A)As drawn to a method of inducing cell death in tumor cells in vivo.

Claims 14-16 and 18 encompass the induction of tumor cell death in vivo comprising the administration of erastin, erastin-B or analogues of erastin. When given the broadest reasonable interpretation, claims 7-9 include the induction of tumor cell death in vivo as well as in vitro. The specification provides evidence that erastin is selectively toxic to tumor cells expressing SV40 small T antigen, and/or h-Ras (pages 30-37, examples 1-3, and Table 1, page 45). the specification provides no objective evidence that the compounds of the instant invention can be used in a method of treating a patient suffering from a naturally occurring tumor. The art teaches that most of the compounds which show promise against cultured tumor cells in vitro, or show promise as an anti-tumor agent in pre-clinical testing fail in clinical trials. Mohanlal (WO 02/40717) teaches (page 1, lines 12-26):

An important reason for the high failure rate in clinical trials is the poor predictive value of currently used screening technologies for biological validation, pharmacological testing, and screening for success or failure of chemical entities and biologicals in clinical trials involving human subjects. These screening technologies are based on in vitro cell-based screening models and in vivo animal models, which often lack or inadequately represent the clinical disease phenotype of the patients in which the tested chemical entities or biologicals are intended to be used in the future.

Therefore, success of these chemical entities or biologicals in these models does not necessarily translate into clinical success in patients. Hence, the majority of chemical entities or biologicals, while successful in these preceding screening and animal models, fail in clinical trials, particularly in late phase II and phase III trials(38). It has been estimated that more than 90% of new chemical entities(NCEs) fail in clinical trials, of which approximately two third fail for pharmacodynamic reasons (lack of efficacy and/or an unacceptable adverse event profile); the remaining third fail for pharmacokinetic reasons (3).

It is noted that an adverse event profile or unfavorable pharmacodynamics can be anticipated by means of an assay with cultured cells.

Given the lack of objective evidence that the claimed compounds are actually effective in patient with a naturally occurring cancer, one of skill in the art would be subject to undue experimentation with out reasonable expectation in order to practice the methods f claims 14-16 and 18 with respect to the treatment of cancer in an individual and with respect to the treatment of cancer in vivo which is encompassed by claims 7-9.

(B)As drawn to a method of preventing cancer in an individual.

Claims 14-16 and 18 are drawn in part to a method of preventing cancer in n individual comprising administering erastin, erastin-B or an analog or erastin. When given the broadest reasonable interpretation, "preventing cancer" reads on the prevention of a cancer in a patient who has yet to develop cancer. In order to do this it would be necessary to identify individuals who will develop cancer before said cancer exists in the individual and to administer the compounds of the invention before said cancer exists. The specification provides o guidance on the selection of individuals who are destined to develop cancer or the optimal timing for the administration of the compounds so as to evoke a prophylactic response. One of skill in the art would be subject to undue experimentation to determine patients who have yet to develop cancer, and the optimal timing of the administration f the instant compounds.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 7-9 are rejected under 35 U.S.C. 102(a) as being anticipated by Dolma et al (Cancer Cell, March 2003, Vol. 3, pp. 285-296).

Claims 7-9 are drawn in part to a method of inducing death in tumor cells, a method of inducing cell death in cells in which the Ras pathway is activated, and a method of inducing death in human cells expressing SV40 small T antigen and h-Ras, respectively comprising contacting the cells with a compound selected from a group including erastin.

Claim 10 is drawn in part to a pharmaceutical composition comprising a pharmaceutically acceptable carrier and erastin.

Dolma et al disclose erastin diluted into DMEM (page 293, under the heading of "Retesting of compounds in a dilution series" which fulfills the limitation of claim 10. Dolma et al disclose that erastin was selectively toxic to small T antigen and Ras in engineered tumorigenic cells (page 287, Table 1, ST=small T antigen SV40), which meets the specific limitations of claim 7-9.

Claims 10 and 12 are rejected under 35 U.S.C. 102(b) as being anticipated by Goldmann et al (WO 01/68641).

Claims 10 and 13 are drawn to pharmaceutical compositions comprising a pharmaceutically acceptable carrier and an analog of erastin and erastin-B respectively. Goldmann et al discloses pharmaceutical compositions (abstract and claim 8) for the treatment of viral diseases, wherein said composition include structure 76 (page 58) which is an analog of both erastin and erastin-B. Goldmann et al do not specifically disclose that structure 76 is selectively toxic to engineered human tumorigenic cells, however, it is noted that the engineered tumorigenic cells do not exclude cells which express the viral promoters or enhancers associated with hepatitis B infection.

In the event that applicant amends claims 10 and 13 to require the engineered cell to express SV 40 small T antigen, h-Ras or a combination thereof, it is noted that the Office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

All claims are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10-6:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Karen A. Canella, Ph.D.
2/20/2007